REMARKS

Claims 1-14 are pending in this application. New Claims 15-20 have been added. Support for the new claims is found in the specification and claims as filed.

Claim Rejection - 35 U.S.C. §103(a)

Claims 1-14 have been rejected under 35 U.S.C. §103(a) as obvious over Lees (US Patent No. 5849301) in view of Penney et al. (US Patent No. 5773007) and Peetermans et al. (US Patent No. 6756040). It is well settled that the Examiner "bears the initial burden of presenting a *prima facie* case of unpatentability..." *In re Sullivan*, 498 F.3d 1345 (Fed. Cir. 2007). Until the Examiner has established a *prima facie* case of obviousness, the Applicant need not present arguments or evidence of non-obviousness. To establish a *prima facie* case of obviousness, the Examiner must establish at least three elements. First, the prior art reference (or references when combined) must teach or suggest all of the claim limitations: "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 165 U.S.P.Q. 494, 496 (CCPA 1970); *see also M.P.E.P. § 2143.03*. Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986); *see also M.P.E.P. § 2143.02*. And finally, the Examiner must articulate some reason to modify or combine the cited references that renders the claim obvious. Merely establishing that the claimed elements can be found in the prior art is not sufficient to establish a *prima facie* case of obviousness:

> As is clear from cases such as *Adams*, a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (emphasis added).

Instead, the Court has made clear that the Examiner must establish a reason one of skill in the art would have combined the elements of the prior art, and that such reason must be more than a conclusory statement that it would have been obvious.

> Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. *See In re Kahn*, 441 F.3d 977, 988 (C.A.Fed.2006) ("[R]ejections on obviousness grounds cannot

> be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1740-1741 (2007).

Affidavits or declarations, when timely presented, containing evidence of criticality or unexpected results, commercial success, long-felt but unsolved needs, failure of others, skepticism of experts, etc., must be considered by the examiner in determining the issue of obviousness of claims for patentability under 35 U.S.C. 103. See M.P.E.P §716.01(a).

Applicants respectfully submit that the pending claims as amended are not obvious under 35 U.S.C. § 103(a) for the reasons detailed below.

The subject matter of Claims 1-14 is directed to methods for preparing conjugate vaccines by reacting an aldehyde activated polysaccharide with a hydrazine activated protein. As acknowledged in the Office Action, Lees does not disclose a pH of 5 to 7 for the conjugation reaction. Lees also does not disclose buffer exchanging the aldehyde-activated polysaccharide to a pH of from 7 to 8 and buffer exchanging the hydrazine-activated protein to a pH of from 10.5 to 11.0 prior to the conjugation reaction. Likewise, neither Penney et al. nor Peetermans et al. includes teachings as to these particular reaction conditions.

As discussed in the Declaration of Che-Hung Robert Lee, there have been no publications or patents describing a method for preparing conjugate vaccines using reductive amination reaction of hydrazide and aldehyde. Likewise, no commercial conjugate vaccine is prepared by reductive amination reaction of hydrazide and aldehyde. It was recognized that methods utilizing protein modification with hydrazide by carbodiimide (EDC) lead to insolubility and precipitation problems in the product. As such, protein modification with hydrazide by EDC was deemed not suitable for use in conjugate vaccine preparation (see, e.g., Schneerson et al, J. Exp. Med. 152:361-376, 1980, page 370, lines 6-7 from bottom; and Chu et al, Infection and Immunity, 40:245-256, 1983, page 246, left column, last paragraph, both submitted in an Information Disclosure Statement dated January 17, 2008). Applicants have developed a method that does not exhibit the insolubility and precipitation problems of EDC-catalyzed hydrazide-activated protein methods. This is accomplished by maintaining the hydrazide-activated protein soluble at pH 10.5-11. Applicants have successfully applied the methodology to the preparation of

conjugate vaccines via a reductive amination reaction with an aldehyde-activated polysaccharide. The covalent linkage created the conjugate vaccines as presently claimed is:

protein-C(=O)-*NH*-*NH*-CH_2-polysaccharide

The italicized letters denote the inserted spacer or linker between the protein and the polysaccharide.

In the Examiner's Response to Applicants' Arguments in the Office Action dated May 19, 2008, the Examiner cites to various passages of Lees as teaching applications method:

> Therefore Lees A teaches a method for preparing a conjugate vaccine, the method comprising: reacting a polysaccharide with an oxidizing agent (sodium periodate), whereby a solution of an aldehyde-activated polysaccharide is obtained; reacting a protein with hydrazine at an acidic pH (see column 6, lines 65-67, column 8 lines 1-3, "reaction of hydrazides"), whereby a solution of a hydrazine-activated protein is obtained; whereby a conjugate is obtained; and neutralizing unreacted aldehyde groups with acidic [sic] acid dihydrazide, whereby a conjugate vaccine capable of stimulating an immune response is obtained, wherein the oxidizing agent comprises NaIO4 (see column 5 line 27-32), wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged with a HEPES buffer, wherein the solution of the aldehyde-activated polysaccharide is buffer exchanged to a pH of from about 7 to about 8 (column 11 lines 55-65, wherein the solution of the hydrazine-activated protein is buffer exchanged with a carbonate buffer (column 11 lines 55-65), wherein the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, wherein a pH of the solution of the hydrazine-activated protein is raised to from about 7.0 to about 11 before the solution of the hydrazine-activated protein is buffer exchanged to a pH of from about 10.0 to about 11.0, whereby substantially all unreacted compounds and unconjugated polysaccharides are removed, yielding a purified conjugate vaccine ...

As noted in the Declaration of Che-Hung Robert Lee, the method of Lees, unlike Applicants' method, uses the cyanylating agent 1-cyano-4-dimethylammoniumpyridinium tetrafluoroborate (CDAP) to activate polysaccharide with cyanate groups at pH 9-10 prior to conjugation to a protein or a limited or minimally hydrazide-activated protein (see Lees, column 7, third paragraph). Lees method using CDAP does not require the protein or hydrazide-activated protein to be maintained at pH 10.5-11 in order to avoid aggregation and precipitation. Furthermore, the covalent linkage created in the conjugated vaccines of the Lees method is:

protein-NH-*C(=NH)*-O-polysaccharide

and/or

limited protein-C(=O)-*NH-NH-C(=NH)*-O-polysaccharide

The fundamental difference between Applicants' method as claimed and that of and Lees is that Applicants' method uses a reductive amination reaction between hydrazide and aldehyde groups, and Lees method uses a reaction between cyanate and amino or hydrazide groups. The reaction employed by Lees and Applicants is different. Because of this fundamental deficiency of the teachings of Lees and its lack of relevance of Lees method to Applicants' method as claimed, a person of ordinary skill in the art would not arrive at Applicants' method as claimed by modifying the teachings of Lees or by combining the teachings of Lees with those of Penney et al. and Peetermans et al. Accordingly, a *prima facie* case of obviousness cannot be established on the basis of Lees, Penney et al., and Peetermans et al.

Even if a *prima facie* case of obviousness could be established on the basis of Lees, Penney et al., and Peetermans et al., it would be rebutted by the unexpectedly superior efficiencies of Applicants' method as claimed. As discussed in the application as filed, conventional methods for the synthesis and manufacture of polysaccharide-protein conjugate vaccines, such as the method disclosed in Lees, employ conjugation reactions with low efficiencies (typically about 20%). Referring to Lees, Table 3, Example 7 specifies a highest efficiency of 20.4%. Most efficiencies reported in Lees are much lower (3.1 to 11.3 %). In contrast, the method as presently claimed exhibits a dramatically higher conjugate yield (typically as high as 60%). The Declaration of Che-Hung Robert Lee provides experimental data demonstrating a three-fold higher efficiency for Applicants' method when compared to the method of Lees. The improved efficiency is due primarily to maintaining the activated protein in a form with improved solubility prior to conjugation. This is accomplished by maintaining the pH of the activated protein at a pH of from 10.0 to 11.0 by buffer exchanging prior to the conjugation step. The conjugation reaction is then conducted under neutral/mild acidic conditions (pH 5 to 7), which results in enhanced solubility of the conjugate. Accordingly, the aforementioned features of the method as claimed are linked to a surprising and advantageous effect, namely, improved efficiency. There is no teaching or suggestion in any of Lees, Penney et al., or Peetermans et al. as to how to achieve such a dramatic improvement in conjugation efficiency. The improved efficiency of Applicants' conjugation method as claimed has other added benefits including, but not limited to, simpler product purification. For example, removal

of small molecule by-products can be achieved by a diafiltration step alone, instead of by a combination of a diafiltration step and a chromatographic separation step as in conventional methods.

None of the cited references suggests that a dramatically improved efficiency, as in Applicants' conjugation method, can be obtained by employing the reaction conditions as recited in Claim 1. Therefore, Applicants respectfully assert that Claims 1-14 are nonobvious over the combination of Lees, Penney et al., and Peetermans et al.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Conclusion

In view of the foregoing, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns that might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 8/20/08

By: _____

Rose M. Thiessen
Registration No. 40,202
Attorney of Record
Customer No. 45311
(619) 235-8550

AMEND

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